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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/658,602	09/08/2003	Enrique Zudaire Ubani	41743.8001.US00	6049
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PERKINS COIE LLP POST OFFICE BOX 1208 SEATTLE, WA 98111-1208			EXAMINER SIMS, JASON M	
			ART UNIT 1631	PAPER NUMBER
			MAIL DATE 07/13/2007	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

<p align="center">Office Action Summary</p>	Application No. 10/658,602	Applicant(s) ZUDAIRE UBANI ET AL.	
	Examiner Jason M. Sims	Art Unit 1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 April 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 9, 11-18, 20-28 and 85-96 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 9, 11-18, 20-28, and 85-96 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>4/13/2007</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's arguments, filed 4/2/2007, have been fully considered but they are not deemed to be persuasive. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Applicants have amended their claims, filed 4/2/2007, and therefore rejections newly made in the instant office action have been necessitated by amendment.

Applicant's cancellation of claims 10 and 19, in the reply filed 4/2/2007 is acknowledged.

Applicant has newly added claims 85-96, which have now been entered.

Claims 9, 11-18, 20-28, and 85-96 are the current claims hereby under examination.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 4/13/2007 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 112

Applicant's arguments, filed 4/2/2007, with respect to the rejection of claims 9-28 under 35 USC 112 second paragraph have been fully considered and are persuasive because of applicant's amendment to the claims. Therefore the rejection of claims 9-28 under 35 USC 112 second paragraph has been withdrawn.

Claim Rejections - 35 USC § 102

Applicant's arguments filed 4/2/2007 have been fully considered but they are not persuasive.

Applicant argues that the present invention eliminates the need for multiple dyes since quantification depends on the melting temperature of each amplicon and the difference between a pre-T_m emission and a post-T_m emission from a single double stranded DNA dye. Applicant further argues that Wittwer et al. discusses using single double stranded DNA dyes, states that multiplexing by color is not possible, and that the invention of Witter et al. uses multiple colors for multiplexing.

Applicant's allegations are moot because although multiplexing by color using a double stranded DNA dye may not be possible, Wittwer et al. did not state that multiplexing using a single double stranded DNA dye was not possible, but in fact states that it is possible by using an analysis of the melting curves. Wittwer et al. at col. 3, lines 1-13 states that product specificity using a single double stranded DNA dye can be made by analysis of melting curves. Therefore, Wittwer et al. indeed recognizes and states that a single double stranded DNA dye can be used for multiplexing by using an analysis of the melting curves and that PCR products can be distinguished by their melting curves. Applicant states in the specification at page 15, paragraph [0047], that combining the property of double stranded DNA dyes with the unique melting temperature of each amplicon has led to unexpected advantages of using these inexpensive dyes to conduct multiplex real-time PCR.

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Additionally, Wittwer et al. at col. 3, lines 14-27, states that multiplexing by color is possible with dual-labeled oligonucleotides, including hairpin probes (molecular beacons). Applicant states at paragraph [0080] "it is considered within the scope of the invention that a primer can be designed to contain a hairpin structure similar to a Molecular Beacon, a reporter dye, or a quencher dye, as long as the reporter dye emits at a different wavelength from the double stranded DNA intercalating dye" and then the amplicon amplified from the designed primer can be individually analyzed and quantified. Moreover, applicant states at paragraph [0085], "a PCR mixture of the present invention may further include one or more fluorescence resonance energy transfer (FRET) based probes" and that "a FRET probe may be used to specifically analyze one or more amplicons among a plurality of amplicons," which is what Wittwer et al. does in real-time as stated in the rejection.

Applicant also alleges that Wittwer et al. does not teach differential emission from the same double stranded DNA dye, but states that multiplexing by color is not possible for dyes binding to double-stranded DNA.

Applicant's argument is not found persuasive as the applicant's invention claims a PCR mixture "comprises" and then lists those elements found in the claimed invention's PCR mixture, such as "a double stranded DNA dye," but does not exclude additional unrecited elements or method steps, such as additional dyes and therefore is not limited to reading on "a single double stranded DNA dye." Furthermore, applicant at paragraph [0052] states "The term "double stranded DNA dye" used herein refers to a fluorescent dye that (1) is related to a fragment of DNA or an amplicon and (2) emits at

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a different wavelength in the presence of an amplicon in duplex formation than in the presence of the amplicon in separation," which is the kind of double stranded DNA dye used in Wittwer et al.

Applicant further argues that the probe in Wittwer et al. is not the entire nucleic acid sample or the product of one or more PCR and that Witter et al. does not teach T_m for PCR products. Applicant further alleges that Wittwer et al. does not teach the T_m for an amplicon in the claimed invention and that an amplicon of the claimed invention refers to a fragment of DNA amplified from a thermostable polymerase using a pair of primers in PCR.

Applicant's allegation are not persuasive as Wittwer et al. at col. 2, col. 3, col. 14, lines 64-67 and col. 15, lines 1-6 discusses a fragment of DNA amplified from a thermostable polymerase using a pair of primers in PCR.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000.

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Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 9, 11-18, 20-28, and 85-96 are rejected under 35 U.S.C. 102(e) as being anticipated by Wittwer et al. (US P/N 6, 472,156).

The claims are directed to a method of real-time detecting and quantifying a first nucleic acid template and a second nucleic acid template in a PCR mixture comprising the steps of thermally cycling a PCR mixture, obtaining first and second emissions, and determining the first and second emission amounts.

Wittwer et al. teaches claims 9, 21, and 85, at col. 1, lines 13-22, col. 2, lines 25-67 and col. 3, lines 1-37, col. 3, lines 40-67, col. 4, lines 1-18, lines 31-35, lines 42-47. Wittwer et al., at col. 1, discusses how the invention relates to multiplex PCR using differential fluorescent emission and differential hybridization melting temperatures, which allows simultaneous analysis. Wittwer et al., at col. 2 and col. 3, discusses step a of claims 9, 21, and 85 a thermal cycling method, using a thermostable polymerase, dyes that bind to double stranded DNA and multiple primers and probes for amplifying multiple sequences of DNA. Wittwer et al. discusses, step b of claims 9, 21, and 85 at col. 3 and col. 4, using at least 2 probe pairs where one member of each pair differentially hybridizes to different alleles and measuring the emission of each of the members at a first temperature and repeating those emission measurements at a second and third temperature, which represents obtaining cycle by cycle at a first MT and a second MT the emissions. Wittwer et al. further discusses part c of claims 9, 21, and 85 in col. 4 at lines 28-35 and 42-47, the different hybridizations having different

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emissions at different Tms and determining the different emissions based on the different Tms, which represents determining cycle by cycle a first emission amount and a second emission amount.

Wittwer et al. teaches claims 11, 12, 22, 23, 86, and 87, at col. 3, lines 4-7.

Wittwer et al. discusses the background to PCR using nucleic acid binding dyes such as ethidium bromide and SYBR Green I, which are double stranded DNA intercalating dyes.

Wittwer et al. teaches claims 13, 24, and 88 at col. 11, lines 66-67 and col. 12, lines 1-5. Wittwer et al. discusses using a PCR primer as a "probe-primer," which represents the double stranded DNA dye as being a primer-based double stranded DNA dye.

Wittwer et al. teaches claims 14, 25, and 89 at col. 12, lines 15-20. Wittwer et al. discusses acceptable fluorophore pairs for use as fluorescein and rhodamine among others.

Wittwer et al. teaches claims 15-18, 26-27, 90-94, and 96 at col. 15, lines 60-67 and col. 16, lines 1-45. Wittwer et al. discusses emission measurements being made every 50 to 10,000 msec and the temperature between measurements varying by 0.01 degrees Celsius per second to 5 degrees Celsius per sec or varying by 0.5 or 1.0 degrees Celsius per second. Wittwer et al. discusses how initial temperatures for initial emission measurements are made at low temperatures and subsequent emission measurements are made at higher temperatures until at least melting temperatures. Therefore the increased increments of temperature ranges ensures at least 3 or more

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emission measurements, which represents increasing the temperature at which emission measurements are taken in the markush ranges specified in the instant claims.

Wittwer et al. teaches claims 20, 28, and 95 at col. 25, lines 65-67. Wittwer et al. discusses using the Lightcycler software for PCR and melting curve analysis, which represent a computer program for calculating first and second emissions.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

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Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jason Sims, whose telephone number is (571)-272-7540.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ram Shukla can be reached via telephone (571)-272-0735.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the Central PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The Central PTO Fax Center number is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

// Jason Sims //

Lee A. Clay
Primary Patent Examiner
7/9/97